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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,768	12/03/2004	Naotò Minamino	62273(71526)	2832

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,768	MINAMINO ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *12-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendments, filed 03 December 2004, 02 February 2005 and 31 May 2005, have been entered in full.

Applicant's election of Group I (claims 1-11) and species election of SEQ ID NO:1 and SEQ ID NO:3 in the reply filed on 07 June 2007 is acknowledged. The Examiner is not obligated to extend the search and examination to the unelected species when the elected species is rejected under *any* of 35 USC 101, 102, 103 or 112 1st, paragraph. None of the instant claims are in condition for allowance.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 12-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07 June 2007.

Claims 1-11 are under examination.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 03 March 2005 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Priority

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed on (03 December 2004).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a peptide which comprises the amino acid sequence of SEQ ID NO:1 and a gene, which encodes said peptide, wherein the gene has a nucleotide sequence of SEQ ID NO:3,

does not reasonably provide enablement for:

a peptide which comprises the amino acid sequence of SEQ ID NO:1, wherein a part of the amino acids are deleted, substituted or added and a gene which encodes said peptide, wherein the gene has a nucleotide sequence of SEQ ID NO:3.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that the present invention is providing novel and useful peptides, which are expressed in the central nervous system and act on calcitonin

receptors. The specification teaches that the present inventors named the novel peptides, calcitonin receptor-stimulating peptides (CRSP), because they act on calcitonin receptors. The specification teaches CRSP as proteins which are expressed in the central nervous system, strongly act on calcitonin receptors, promote a cAMP productivity of cells, incorporate sodium ion in a concentration-dependent manner, suppress the uptake of calcium ions and suppress cell proliferation (page 4, 1st paragraph-page 5). The specification teaches that the present invention comprise peptides having homology to a calcitonin gene-related peptide (CGRP), therefore, they may be expected to have the physiological activity similar to that of CGRP which include, strongly acting on calcitonin-gene related peptide receptors, inducing relaxation of blood vessels, promoting diuresis and altering the proliferation potency of vascular endothelial cells, vascular smooth muscles and fibroblasts (page 5). The specification teaches that CRSP of the present invention has an amino acid sequence homology to pig CGRP, human CGRP-I and human CGRP-II of 71%, 63% and 71%, respectively (page 18).

The specification teaches the extraction and isolation of CRSP from pig brain, which has the following sequence as SEQ ID NO:1 with an amino acid sequence of CRSP-Gly shown in SEQ ID NO:2 (page 41). The specification teaches that pig CRSP increases an intracellular adenylyl cyclase activity of LLC-PK1 cells derived from pig renal epithelial cells in a concentration-dependent manner. The activity was stronger than pig calcitonin or pig CGRP (page 20, page 45 and Figure 4). The specification teaches that pig CRSP activated an amyloride-sensitive Na/H co-transporter on LLC-

PK1 cells whereby incorporation of sodium into cells was promoted and incorporation of calcium into cells was suppressed (page 22, pages 45-47 and Figures 5-7). The specification teaches the suppression of LLC-PK1 cell proliferation in the presence of pig CRSP (pages 22-23 and page 47 and Figures 8-9). The specification teaches the transfection of pig calcitonin receptor in COS and renal cells and increased production of cAMP by pig CRSP stimulation (pages 23-25 and page 48 and Figures 10-12). The specification teaches the administration of pig CRSP to the carotid artery of rats. Pig CRSP lowered the calcium concentration in the blood of rats (pages 25-26, page 48 and Figure 13).

The instant claims are not supported by an enabling disclosure because the specification does not teach how to make and use any mutant/variant of pig calcitonin receptor stimulating peptide (CRSP). The specification teaches pig CRSP as SEQ ID NO:1. The instant claims are drawn to SEQ ID NO:1 wherein any amino acids are deleted, substituted or added, while having the recited functional properties (i.e. suppressing cell proliferation, promoting cAMP production, etc). The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence, which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of

these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of amino acid deletions, substitutions and additions, results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Please see Wells (1990, Biochemistry 29:8509-8517).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a pharmaceutical composition comprising pig CRSP (SEQ ID NO:1) and a pharmaceutical acceptable carrier. The term "pharmaceutical" is used in the preamble of the instant claims. The intended use of the claim as a pharmaceutical is imputed to mean intended *in vivo* therapeutic use. The instant claims are not supported by an enabling disclosure, because the specification fails to teach CRSP as a diuretic agent, an analgesic or a hypotensive agent. The specification fails to teach the use of CRSP for treating osteoporosis, cancer, suppressing appetite or treating restenosis. The specification fails to teach the administration of CRSP to a subject suffering from or susceptible to osteoporosis. The specification fails to provide any guidance on the *in vivo* use of the claimed composition to treat any of the recited disease and/or condition. No examples of treatment are provided. The instant specification fails to employ applicable animal models or other assays that would correlate with *in vivo* treatment of the recited conditions. The instant specification teaches certain activities of pig CRSP *in vitro*. However, it could not be predicted that the cell culture data presented in the specification would be in any way correlative with therapeutic agents for *in vivo* treatments. The specification teaches decreased blood calcium levels in rats upon CRSP administration but this is not tantamount to treatment of the claimed assortment of diseases.

Lastly, the specification is not enabling for the term "preventive" or "prevents". Prevent means to completely stop a condition from occurring. "Prevention" is not a relative term, it is total. The specification is not enabled for a method of preventing or stopping any disease or condition. A very high degree of evidence is required, which is

accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

Due to the large quantity of experimentation necessary to show a correlation between the pharmaceutical composition comprising pig CRSP (SEQ ID NO:1) and treatment and/or prevention of a specific disease in a subject, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite any parameters for the treatment and/or prevention of the recited diseases, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for SEQ ID NO:1 and SEQ ID NO:3, but not variants, derivatives or mutants of SEQ ID NO:1 or SEQ ID NO:3.

The specification does not place any limit on the number of substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO:1 or SEQ ID NO:3. The specification does not provide any guidance as to what changes should be made and which regions of the instant protein are functionally and structurally critical. There is no description of variants of SEQ ID NO:1 that exist, while still maintaining

function. Specific, not general guidance is what is needed. The disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is variant, SEQ ID NO:1 and SEQ ID NO:3 are insufficient to describe the genus. The disclosure fails to provide a representative number of species to describe the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of SEQ ID NO:1 and SEQ ID NO:3, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Due to the breadth of the claim genus and lack of the definitive structural features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed genus. Therefore, only SEQ ID NO:1 and SEQ ID NO:3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
8/9/07

Marianne P. Allen

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PRIMARY EXAMINER
AU1647 8/10/07